seek nicotine primarily for its systemic pharmacological effects and not for its acute sensory effects. In contrast to cigarette smoke, aqueous nicotine spray does not provide the user any pleasing sensory characteristics. In fact, the spray can be irritating and unpleasant to use, and excessive use can cause ulcerations of the nasal mucosa. Notwithstanding the unpleasantness of the nicotine delivery mechanism and the presence of painful ulcerations that were further aggravated by its continued use, the spray was used to maintain nicotine dependence for some participants in clinical trials submitted to FDA.[194]

Studies of nicotine replacement therapies also demonstrate efficacy in maintaining abstinence from smoking.[195] The ability of nicotine to promote abstinence, even when delivered through the skin, without any taste or flavor, demonstrates its key role as a reinforcer of tobacco consumption. Based on these data, among others, organizations with expertise in pharmacology and addiction have determined that cigarettes and smokeless tobacco deliver pharmacologically active doses of nicotine. In the 1986 analysis of smokeless tobacco, the Surgeon General determined that smokeless tobacco use can be addictive.[196] In 1988, after an even more extensive consideration of the potential addictiveness of nicotine, the Surgeon General determined that: (1) "cigarettes and other forms of tobacco are addicting;" (2) "nicotine is the drug in tobacco that causes

---

[194] FDA Drug Abuse Advisory Committee Background Information (Aug. 1, 1994), Joint Abuse Liability Review of Nicotine Nasal Spray. *See* AR (Vol. 9 Ref. 117).

[195] *See* appendix 1 to Jurisdictional Analysis. *See* AR (Vol. 1 Appendix 1).

[196] Department of Health and Human Services, Public Health Service, *The Health Consequences of Using Smokeless Tobacco: A Report of the Advisory Committee to the Surgeon General, 1986,* NIH Publication No. 86-2874 (Bethesda MD: DHHS, PHS, 1986) (hereinafter cited as Surgeon General's Report, *Smokeless Tobacco,* 1986), at viii. *See* AR (Vol. 128 Ref. 1591).

addiction;" and (3) "the pharmacological and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin and cocaine."[197] On August 2, 1994, FDA's Drug Abuse Advisory Committee, an independent group composed primarily of experts on addiction science, concluded that nicotine as delivered by commonly used tobacco products can produce strong physiological effects, including addiction.[198]

6. Conclusion

Nicotine is addictive and produces foreseeable psychoactive and pharmacological effects in a substantial proportion of tobacco users. This conclusion is so robust—and the evidence for it is so voluminous—that every major public health organization and relevant scientific authority in the world is in agreement. It is FDA's responsibility to base its regulatory actions on well-founded and accepted scientific facts. In this case, FDA believes that a very strong scientific basis exists on which to conclude that it is foreseeable that nicotine will produce pharmacological effects in a substantial number of tobacco consumers and that those consumers will use tobacco products to satisfy their addiction and to obtain the other pharmacological effects of nicotine. To conclude otherwise would not be credible.

[197] Surgeon General's Report, 1988, at 13-17. *See* AR (Vol. 129 Ref. 1592).

[198] Transcript to the FDA Drug Abuse Advisory Committee, Meeting 27, "Issues Concerning Nicotine-Containing Cigarettes and Other Tobacco Products" (Aug. 2, 1994), at 336-342. *See* AR (Vol. 255 Ref. 3445).

7. Response to Additional Comments

a. Comments on the Professional Consensus That Nicotine Is Addictive

1. More than 150 professional health organizations or chapters, representing over 600,000 individuals and organizations, commented on whether nicotine is addictive. Virtually all concluded that it is. These groups include the following:

- The American Cancer Society
- The American College of Physicians
- The American Heart Association
- The American Lung Association
- The American Medical Association
- The American Psychiatric Association
- The American Psychological Association
- The American Society of Addiction Medicine
- The College on Problems of Drug Dependence
- The Society of General Internal Medicine
- The Society for Head and Neck Surgeons
- The Society for Research on Nicotine and Tobacco
- The Virginia Society of Hospital Pharmacists

FDA also notes that, of the more than 1,100 physicians, pharmacists, and other health professionals who commented on whether nicotine is addictive, virtually all agreed that it is.

The Agency concurs with the unanimous conclusion of these organizations, most of which have expertise in this area. FDA notes that organizations with vast experience

examining other addictive drugs reached the same conclusion as organizations with vast experience studying nicotine. The former organizations include the American Psychiatric Association, the American Society of Addiction Medicine, the National Institute on Drug Abuse, and the World Health Organization. The latter include the American College of Chest Physicians and the Surgeon General's expert committees on tobacco.

2. The tobacco industry disputes the process by which the American Psychiatric Association concluded that nicotine is addictive. The industry quotes several critical comments about the *Diagnostic and Statistical Manual* to suggest that the entire DSM structure of classifying all psychiatric diagnoses is flawed. This position, held by a small minority of psychiatrists, has been decisively rejected by the profession as a whole. The DSM-IV is now used throughout the world to classify psychiatric disorders, including drug dependence.

FDA notes that, aside from this argument against the American Psychiatric Association, the industry does not dispute the expertise or decision-making capabilities of any of the other medical authorities originally cited by FDA. These authorities—which unanimously have concluded that nicotine is addictive—include the U.S. Surgeon General, the World Health Organization, the American Medical Association, the American Psychological Association, the Royal Society of Canada, and the Medical Research Council of the United Kingdom.

b. Comments on the Definition of Addiction

1. Several tobacco industry comments argue that cigarettes and smokeless tobacco are not addictive under a now-discarded definition of addiction developed in the 1950's and used by the U.S. Surgeon General in 1964.

FDA disagrees with these comments. First, the tobacco industry borrows only selectively from the 1950's definition of addiction, emphasizing only certain criteria from that definition. Second, while the scientific community has rejected this historical definition in part because it failed to clearly classify cocaine and amphetamines as addictive, *see* section II.A.3.b., above, subsequent evidence has shown that nicotine would now qualify as addictive *even by this outdated definition.* The criteria cited by the Surgeon General,[199] which were not met by nicotine on the basis of data available in the early 1960's, are all met on the basis of data available today. These include the following:

- Surgeon General's 1964 conclusion: No overpowering compulsion to use the drug.

  Subsequent data: Ample documentation exists today that persons dependent upon cocaine, heroin, or alcohol find it as difficult to abstain from tobacco as from these other drugs and that persons who know that their lives are in imminent danger from smoking nevertheless continue to smoke.[200]

- Surgeon General's 1964 conclusion: No tendency to increase the dose.

---

[199] Department of Health, Education, and Welfare, Public Health Service, *Smoking and Health: Report of the Advisory Committee to the Surgeon General of the Public Health Service* (Washington DC: GPO, 1964), at 349-352. *See* AR (Vol. 43 Ref. 156).

[200] Henningfield JE, Cohen C, Slade JD, Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991;86:565-569. *See* AR (Vol. 277 Ref. 3904).

Kozlowski LT, Wilkinson DA, Skinner W, *et al.*, Comparing tobacco cigarette dependence with other drug dependencies, *Journal of the American Medical Association* 1989;261:898-901. *See* AR (Vol. 84 Ref. 350).

West R, Himbury S, Smoking habits after laryngectomy, *British Medical Journal* 1985;291:514-515. *See* AR (Vol. 6 Ref. 59).

Davison G, Duffy M, Smoking habits of long term survivors of surgery for lung cancer, *Thorax* 1982;37:331-333. *See* AR (Vol. 6 Ref. 58).

Subsequent data: We now know that only about 10% of cigarette smokers are able to sustain a level of intake of five or fewer cigarettes per day. For example, one study found that 90% of people who smoke escalate to daily doses of five or more cigarettes.[201] Cigarettes are similar to morphine-like drugs in that, when either substance is readily available to the user, intake often escalates over a period of months or years and then stabilizes at a level that may vary little from day to day for many years.[202]

- Surgeon General's 1964 conclusion: No physical dependence on the effects of the drug.

  Subsequent data: The documentation that nicotine produces physical dependence has now been provided by scores of clinical treatment studies and laboratory studies with humans and animals.[203] There is a characteristic

---

[201] Benowitz NL, Cigarette smoking and nicotine addiction, *Medical Clinics of North America* 1992;76(2):415-437. *See* AR (Vol. 535 Ref. 96, vol. III.A).

Henningfield JE, Cohen C, Slade JD, Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991;86:565-569. *See* AR (Vol. 277 Ref. 3904).

[202] Jaffe JH, Drug addiction and drug abuse, in *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* 8th ed. (New York: Pergamon Press, 1990), chap. 22 (522-573). *See* AR (Vol. 535 Ref. 96, vol. III.G).

[203] Henningfield JE, Cohen C, Slade JD, Is nicotine more addictive than cocaine? *British Journal of Addiction* 1991;86:565-569. *See* AR (Vol. 277 Ref. 3904).

Kozlowski LT, Wilkinson DA, Skinner W, *et al.*, Comparing tobacco cigarette dependence with other drug dependencies, *Journal of the American Medical Association* 1989;261:898-901. *See* AR (Vol. 84 Ref. 350).

Surgeon General's Report, 1988, at 145-240. *See* AR (Vol. 129 Ref. 1592).

Corrigall WA, Herling S, Coen KM, Evidence for a behavioral deficit during withdrawal from nicotine treatment, *Pharmacology Biochemistry and Behavior* 1989; 33:559-562. *See* AR (Vol. 139 Ref. 1626).

tobacco withdrawal syndrome that has been recognized by leading medical organizations.[204]

- Surgeon General's 1964 conclusion: Detrimental effects on society are not well documented.

  Subsequent data: The detrimental effects on smokers themselves were recognized in 1964; however, it was not until the 1980's that the direct adverse effects of smoking upon nonsmokers and the fetuses of pregnant smokers were unequivocally documented.[205] Moreover, it is now recognized that nicotine has a severe adverse economic impact on many aspects of society.[206]

In addition to these four specific criteria, the Surgeon General in 1964 mentioned several other reasons for failing to categorize nicotine as addicting. These conclusions and the current data are as follows:

- Surgeon General's 1964 conclusion: Cigarette smokers did not become intoxicated.

Levin ED, Morgan MM, Galvez C, *et al.*, Chronic nicotine and withdrawal effects on body weight and food and water consumption in female rats, *Physiology and Behavior* 1987; 39:441-444. *See* AR (Vol. 278 Ref. 3932)

[204] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. (Washington DC: American Psychiatric Association, 1994), at 244-245. *See* AR (Vol. 37 Ref. 8).

[205] Department of Health and Human Services, Office on Smoking and Health, *The Health Consequences of Involuntary Smoking: A Report of the Surgeon General* (Atlanta: DHHS, 1986) (hereinafter cited as Surgeon General's Report, *Involuntary Smoking*, 1986). *See* AR (Vol. 128 Ref. 1591).

[206] McGinnis JM, Foege WH, Actual causes of death in the United States, *Journal of the American Medical Association* 1993;270(18):2207-2212. *See* AR (Vol. 2 Ref. 15-1).

Hearing on Preventive Health: An Ounce of Prevention Saves a Pound of Cure, Before the Special Committee on Aging, U.S. Senate, 103d Cong., 1st Sess. 2 (May 6, 1993) (statement of Roger Herdman, Maria Hewitt, Mary Laschober on smoking-related deaths and financial costs: Office of Technology Assessment Estimates for 1990). *See* AR (Vol. 170 Ref. 2024).

Hodgson TA, Cigarette smoking and lifetime medical expenditures, National Center for Health Statistics, *Milbank Quarterly* 1992;70(1):81-125. *See* AR (Vol. 19 Ref. 22).

Subsequent data: It is now well understood that nicotine can intoxicate, intoxication is a sign of nicotine overdose, and first-time users often become intoxicated.[207] The ability of nicotine to produce strong physiological and behavioral effects, including death at high doses, is no less than that of amphetamine or morphine.[208] In practice, intoxication is rarely evident in regular users because they have developed an extremely high level of tolerance to this effect of nicotine.[209]

- Surgeon General's 1964 conclusion: Subjective effects of nicotine itself were not well documented. The 1942 study by Johnston showing that intravenous nicotine could mimic the effects of smoking[210] was apparently given little weight because the study did not have the appropriate control conditions to rule out bias.

  Subsequent data: By the 1980's and 1990's, many properly controlled studies using nicotine delivered intravenously, intranasally, and by inhalation essentially confirmed Johnston's findings.[211]

---

[207] Surgeon General's Report, 1988, at 593-594. *See* AR (Vol. 129 Ref. 1592).

[208] *Id.* at 272-274, 594.

[209] *Id.* at 593-595.

[210] Johnston LM, Tobacco smoking and nicotine, *Lancet* 1942;2:742. *See* AR (Vol. 278 Ref. 3947).

[211] *See, e.g.,* Jones RT, Farrell TR III, Herning RI, Tobacco smoking and nicotine tolerance, in *Self-Administration of Abused Substances: Methods for Study,* ed. Krasnegor NA, NIDA Research Monograph 20 (Rockville MD: National Institute on Drug Abuse, 1978), at 202-208. *See* AR (Vol. 41 Ref. 88).

Henningfield JE, Miyasato K, Jansinski DR, Abuse liability and pharmacodynamic characteristics of intravenous and inhaled nicotine, *Journal of Pharmacology and Experimental Therapeutics* 1985;234:1-12. *See* AR (Vol. 39 Ref. 69).

Pomerleau CS, Pomerleau OF, Euphoriant effect of nicotine in smokers, *Psychopharmacology* 1992;108:460-465. *See* AR (Vol. 87 Ref. 426).

Perkins KA, Grobe JE, Epstein LH, *et al.*, Chronic and acute tolerance to subjective effects of nicotine, *Pharmocology, Biochemistry and Behavior* 1993;45:375-381. *See* AR (Vol. 271 Ref. 3728).

- Surgeon General's 1964 conclusion: No well-controlled demonstration that nicotine substitution could facilitate tobacco abstinence.

  Subsequent data: The absence of a nicotine-delivering medication effective in helping people to achieve abstinence was also noted in the 1964 report. There is now powerful evidence that products devoid of any tobacco constituent except nicotine are effective aids to smoking cessation and to providing relief of withdrawal symptoms.[212]

- Surgeon General's 1964 conclusion: Personality deficit criteria did not appear satisfied.

  Subsequent data: It was noted that not categorizing tobacco use as an addiction avoided the inference that smokers would be considered to have "serious personality defects" under the definition of addiction then in place. We now understand that many people who develop addictions to cocaine, heroin, alcohol, or nicotine have no documented underlying personality disorder. Rather, the major cause of addiction is

---

Perkins KA, Grobe JE, Epstein LH, *et al.*, Effects of nicotine on subjective arousal may be dependent on baseline subjective state, *Journal of Substance Abuse* 1992;4:131-141. *See* AR (Vol. 348 Ref. 5516).

Sutherland G, Stapleton JA, Russell MAH, *et al.*, Randomised controlled trial of nasal nicotine spray in smoking cessation, *Lancet* 1992;340:324-329. *See* AR (Vol. 91 Ref. 527).

Sutherland G, Russell MA, Stapleton J, *et al.*, Nasal nicotine spray: a rapid nicotine delivery system, *Psychopharmacology* 1992;108:512-518. *See* AR (Vol. 91 Ref. 526).

[212] Fagerstrom KO, Sawe U, Tonnesen P, Therapeutic use of nicotine patches: efficacy and safety, *Journal of Drug Development* 1993;5:191-205. *See* AR (Vol. 76 Ref. 156).

Fiore MC, Smith SS, Jorenby DE, *et al.*, The effectiveness of the nicotine patch for smoking cessation: a meta-analysis, *Journal of the American Medical Association* 1994;271:1940-1947. *See* AR (Vol. 6 Ref. 64-1).

Fiore MC, Jorenby DE, Baker TB, *et al.*, Tobacco dependence and the nicotine patch, *Journal of the American Medical Association* 1992;268:2687-2694. *See* AR (Vol. 351 Ref. 5609).

Surgeon General's Report, 1988, at 208. *See* AR (Vol. 129 Ref. 1592).

the presence of a psychoactive, reinforcing drug and adequate access to the drug to enable the development and sustenance of addiction.

Thus, it is virtually certain that tobacco use would be considered an addiction under the definition used by the Surgeon General in 1964. Indeed, FDA notes that a study sponsored by the tobacco industry in 1963 concluded that tobacco was addictive under the same definition used by the Surgeon General in 1964.[213]

2. The tobacco industry observes that definitions of addiction from several medical authorities are not identical, quotes several experts stating that whether tobacco is addictive depends on the definition of addiction, and presents excerpts from several scientific publications to suggest that no precise definition of addiction exists. The industry also argues that the use of the word "addiction" rather than "dependence" is political and claims that the modern definition of addiction is motivated by public health goals, morality, and lawsuits. The industry concludes that the modern definition of addiction is inappropriate for use in considering whether a product is a drug under the Act.

FDA disagrees. As discussed in section II.A.3.b., above, there is remarkable consensus among medical authorities around the world on the meaning of addiction. The subtle variations among written definitions reflect wording and emphasis, not significant differences in concepts; such variations are not surprising, given that medical organizations often write their own definitions of diseases and disease progression. International consistency on the meaning of addiction is demonstrated by the fact that all relevant

[213] Knapp PH, Bliss CM, Wells H, Addictive aspects in heavy cigarette smoking, *American Journal of Psychiatry* 1963;119:966. *See* AR (Vol. 528 Ref. 97, appendix 16).